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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte OSVALDO A. FLORES, JAY GROBLER,
EDWARD M. MURRAY, and PAUL D. ZUCK

Appeal 2009-008871
Application 10/510,912
Technology Center 1600

Decided: January 14, 2010

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a hepatitis C virus (HCV) replicon. The Examiner has rejected the claims for obviousness and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The Specification discloses "assays employing … a chimeric HCV replicon containing a 3'UTR based on the HCV-1a 3' UTR," which can be used "to measure HCV replicon activity and the affect [sic] of compounds on such activity" (Spec. 2: 14-18).

Claims 19, 20, 28, 29 and 31-38 are on appeal.[1] Claims 19 and 20 are representative and read as follows:

Claim 19: A chimeric Hepatitis C Virus (HCV) replicon comprising at least two HCV regions, wherein the regions are from different HCV strains and wherein at least one of the regions is a HCV-1a 3' UTR.

Claim 20: The chimeric HCV replicon of claim 19, wherein at least one of said regions consists of a non-structural region from a clinical isolate of HCV.

The claims stand rejected under 35 U.S.C. § 103(a) as follows:

- Claims 19, 20, 28, 29, 31-34, 37, and 38 in view of De Francesco,[2] Rice I,[3] Rice II,[4] Melnick,[5] and Li;[6]
- Claims 35 and 36 in view of De Francesco, Rice I, Rice II, Melnick, Li, and Hawkins.[7]

The Examiner also provisionally rejected claims 19, 20, 28, 29, 31-34, 37, and 38 for obviousness-type double patenting in view of claims 19 and

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[1] Claims 21, 39-41 and 43 have been indicated to be allowable (Office Action mailed March 26, 2008).
[2] De Francesco et al., WO 02/059321 A2, Aug. 1, 2002
[3] Rice et al., US 6,297,003 B1, Oct. 2, 2001
[4] Rice et al., WO 01/89364 A2, Nov. 29, 2001
[5] Melnick et al., US 6,063,562, May 16, 2000
[6] Li et al., US 2004/0018529 A1, Jan. 29, 2004
[7] Hawkins et al., US 5,783,669, July 21 1998

20 of copending application no. 10/543,633 (Ans. 7-8). Appellants do not dispute the rejection, but state that they "will consider submitting a Terminal Disclaimer should claims in this application or application Serial No. 10/543,633 be deemed allowable" (Appeal Br. 17). Since Appellants have not disputed the merits of the provisional double patenting rejection, we summarily affirm it.

OBVIOUSNESS I

Issue

The Examiner has rejected claims 19, 20, 28, 29, 31-34, 37, and 38 under 35 U.S.C. § 103(a) in view of De Francesco, Rice I, Rice II, Melnick, and Li. The claims have been argued in two groups: claims 28 and 29 stand or fall with claim 19, and claims 31-34, 37, and 38 stand or fall with claim 20. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that De Francesco discloses HCV replicons that "comprise an HCV 3' UTR sequence, and indicates that any such sequence may be used" (Ans. 3). The Examiner also finds that De Francesco "indicates that the non-structural protein sequences used in the replicon may include proteins, including NS5B proteins, from different HCV strains" (*id.* at 4). The Examiner finds that "Rice I teaches the sequences of several HCV 3' UTRs, including the sequences of several variants of the HCV 1a isolate H77. … The reference also indicates that such sequences would be useful for the construction of HCV replicons which could be used for screening for inhibitors of HCV replication." (*Id.*) The Examiner concludes that "it would have been obvious to those of ordinary skill in the art to use the 3' UTRs of Rice I for the production of HCV replicons as suggested by De Francesco … because the art indicates that the 3' UTRs of Rice I are

functional equivalents for the UTR sequences provided in De Francesco" (*id.*). With regard to claim 20, the Examiner finds that Rice II, Melnick and Li would have suggested including a coding sequence for a nonstructural protein from a clinical isolate of HCV in De Francesco's HCV replicon (*id.* at 5-6).

Appellants contend that "there is no specific suggestion to use a HCV-1a 3'UTR" from the combination of De Francesco and Rice I (Appeal Br. 11). With regard to claim 20, Appellants contend that none of Rice II, Melnick or Li suggest the use of a sequence from an HCV clinical isolate (*id.* at 13-15).

The issues with respect to this rejection are:

Does the evidence of record support the Examiner's conclusion that the cited references suggest a chimeric HCV replicon comprising regions from different HCV strains, and including an HCV-1a 3' UTR?

and

Does the evidence of record support the Examiner's conclusion that the cited references suggest a chimeric HCV replicon comprising regions from different HCV strains, including an HCV-1a 3' UTR and a nonstructural region from a clinical isolate of HCV?

Findings of Fact

1. De Francesco discloses HCV replicons (De Francesco 6).

2. De Francesco discloses that a "basic HCV replicon is a subgenomic construct containing an HCV 5' UTR- PC region, an HCV NS3-NS5B polyprotein encoding region, and a HCV 3' UTR" (*id.* at 10).

3. De Francesco discloses that the "HCV 3' UTR assists HCV replication. HCV 3' UTR includes naturally occurring HCV 3' UTR and functional derivatives thereof." (*Id.*)

4. De Francesco discloses that the

> NS3-NS5B polyprotein encoding region provides for a polyprotein that can be processed in a cell into different proteins. Suitable NS3-NS5B polyprotein sequences that may be part of a replicon include those present in different HCV strains and functional equivalents thereof resulting in the processing of NS3-NS5B to a produce functional replication machinery.

(*Id.*)

5. De Francesco discloses that HCV replicons can be used "to study HCV replication and expression, to study HCV and host cell interactions, to produce HCV RNA, to produce HCV proteins, and to provide a system for measuring the ability of a compound to modulate one or more HCV activities." (*Id.* at 6.)

6. Rice I discloses that "several major HCV genotypes are distributed throughout the world.... Those of greatest importance in the U.S. are genotype 1, subtypes 1a and 1b." (Rice I, col. 3, l. 65-col. 4, l. 5).

7. Rice I discloses that

> there exists a need in the art for [the] identification of ... the 3' terminal sequence of HCV which can be incorporated into a full-length cDNA clone capable of yielding infectious RNA transcripts, which then can be used as target sequences for the production of attenuated HCV for vaccines, and which can be used as targets for therapeutic compositions.

(*Id.* at col. 7, ll. 5-11.)

8. Rice I discloses that its Figure 3 shows "the sequence ... of HCV-H 3' clones" (*id.* at col. 11, ll. 20-25).

9. The Examiner finds, and Appellants do not dispute, that Figure 3 of Rice I discloses the HCV 3' UTRs from several variants of HCV 1a isolate H77 (Ans. 4).

10. Rice II discloses that

> the RNA-dependent RNA polymerase of HCV (NS5B) is believed to lack a 3'-5' exonuclease proof reading activity for removal of misincorporated bases. Replication is therefore error-prone, leading to a "quasi-species" virus population consisting of a large number of variants. ... [I]n a chronically infected individual, changes in the virus population occur over time...; and these changes may have important consequences for disease.

(Rice II 7: 14-23.)

11. Melnick discloses screening methods related to identifying drug resistance in HIV (Melnick, abstract).

12. Melnick discloses that

> [o]ne application of the above-described method is in the screening of prospective drugs against biologically-active mutant forms of the protease obtained in a clinical setting. Such mutant proteases may be obtained, for example, from tissue or blood samples of infected patients, from clinical isolates of pathogen grown in cell culture, or from amplified protease-encoding RNA or DNA obtained from an infected patient and expressed in an in vitro translation system.

(*Id.* at col. 11, ll. 6-13.)

13. Li discloses that "[a]lthough protease inhibitors have shown great potential for the treatment of AIDS, it is complicated by the rapid emergence of HIV strains that are resistant to protease inhibitors" (Li, ¶ 0009).

14. Li discloses an assay that "can be adapted for the rapid screening of various clinical isolates of HIV for resistance to a panel of protease inhibitors" (*id.*).

15. Li discloses that, like HIV, "hepatitis C virus (HCV) also codes for a protease that is responsible for the proteolytic processing of a single large polyprotein precursor made by the virus" and that viral proteases "are often a target of intense research activity for the development of therapeutics" (*id.*).

Principles of Law

"[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

Analysis

Claim 19 is directed to a chimeric HCV replicon comprising at least two HCV regions from different HCV strains, where one of the regions is an HCV-1a 3' UTR.

De Francesco and Rice I disclose that HCV replicons that include a 3' UTR, are useful for the evaluation of anti-HCV therapeutics. Rice I also discloses that subtype 1a is a major subtype of HCV in the United States and discloses the sequence of several HCV-1a 3' UTRs. De Francesco discloses that non-structural genes from different subtypes may be used in replicons. In view of these disclosures, it would have been obvious to one of ordinary skill in the art to include an HCV-1a 3' UTR in De Francesco's HCV replicon (i.e., a replicon that also contains a non-structural gene from another subtype) because De Francesco discloses that any HCV 3' UTR can

be used and Rice I teaches that subtype 1a is one of the major subtypes of HCV in the United States.

Appellants argue that the cited references do not suggest a chimeric replicon with a HCV-1a 3' UTR because "there is no specific suggestion to use a HCV-1a 3'UTR" in De Francesco or Rice I (Appeal Br. 11)

This argument is not persuasive. Appellants concede that five of the seventeen 3' UTR sequences disclosed by Rice I are from HCV-1a (Appeal Br. 11). In addition, as discussed above, Rice I discloses that the HCV-1a subtype is one of the predominant subtypes in the United States. Thus, Rice I would have made obvious the use of replicons including the HCV-1a 3' UTR to evaluate potential therapeutic agents. Further, De Francesco discloses that components from different HCV subtypes can be combined in the same HCV replicon. Thus, Rice I and De Francesco would have made obvious to persons of ordinary skill in the art an HCV replicon containing an HCV-1a 3' UTR and at least one sequence region from another HCV subtype.

Claim 20 depends on claim 19 and further requires that "at least one of said [HCV] regions consists of a non-structural region from a clinical isolate of HCV."

The Examiner relies on De Francesco and Rice I, as discussed above (Ans. 5). The Examiner finds that Rice II discloses that HCV evolves over time in an infected patient (*id.*), and finds that Melnick and Li disclose the screening of drugs against clinical isolates of HIV because it evolves over time (*id.*). The Examiner concludes that it would have been obvious to those of ordinary skill in the art to construct HCV replicons with sequences from clinical isolates to screen therapeutic agents (*id.* at 5-6) in order to identify

antiviral agents effective against the viral strains in the clinical isolates. We agree with the Examiner's reasoning.

Appellants argue that the cited references do not suggest a replicon with "a non-structural region from a clinical isolate of HCV" because Rice II highlights changes occurring in the E2 glycoprotein, a structural protein, and because Rice II does not specifically suggest clinical isolates of HCV (Appeal Br. 12-16).

These arguments are not persuasive. Rice II discloses the general problem of viruses evolving over time, and Melnick and Li specifically discuss clinical isolates to evaluate the evolution of proteases (encoded by non-structural genes) to become drug resistant. Li discloses that replication of HCV also involves a viral protease. Thus, the teachings of the combined references would have suggested an HCV replicon that includes a non-structural gene from a clinical isolate of HCV.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the cited references suggest a chimeric HCV replicon comprising regions from different HCV strains, and including an HCV-1a 3' UTR. The evidence of record also supports the Examiner's conclusion that the cited references suggest a chimeric HCV replicon comprising regions from different HCV strains, including an HCV-1a 3' UTR and a nonstructural region from a clinical isolate of HCV.

OBVIOUSNESS II

The Examiner has rejected claims 35 and 36 under 35 U.S.C. § 103(a) in view of De Francesco, Rice I, Rice II, Melnick and Li, and Hawkins. The

Examiner relies on De Francesco, Rice I, Rice II, Melnick and Li for the teachings discussed above, and concludes that Hawkins would have made obvious the additional limitations of claims 35 and 36 (Ans. 6-7). We agree with the Examiner's reasoning and conclusion.

Appellants do not dispute that Hawkins would have suggested the limitations added to claim 20 by claims 35 and 36, but contend that Hawkins does not cure the deficiencies of De Francesco, Rice I, Rice II, Melnick and Li (Appeal Br. 16). This argument is not persuasive for the reasons discussed above.

SUMMARY

We affirm the rejection of claims 19, 20, 28, 29 and 31-38 under 35 U.S.C. § 103(a) and the rejection of claims 19, 20, 28, 29 and 31-34, 37 and 38 for obviousness-type double patenting.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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